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Male ob/ob mice (Jackson Laboratories, Bar Harbor, Me.) at 8 weeks of age were randomized into 5 groups as described in Example 12. The mice were administered vehicle, Pegylated Compound 2 and Compound 170 subcutaneously twice weekly (BIW) as follows (n=12 for each group): 1) Vehicle (250 mM sucrose/20 mM Tris, pH 8.3); 2) Pegylated Compound 2, 8.14 nmol/kg (0.15 mg/kg); 3) Compound 170, 81.45 nmol/kg (1.5 mg/kg); 4) Pegylated Compound 2, 81.45 nmol/kg (1.5 mg/kg); and 5) Compound 170, 81.45 nmol/kg (1.5 mg/kg). Body weight, plasma glucose, triglycerides, insulin, nonesterified fatty acids (NEFA), β -OH-butyrate, total adiponectin, and high molecular weight (HMW) adiponectin were determined throughout the 21 day dosing period in the fed state. Glycated hemoglobin (HbA1c) in whole blood was determined at study start and termination. Liver weight and liver triglycerides were determined at study termination. Liver histology was performed with the left lateral lobe of the liver to evaluate hepatocyte steatosis. The tissue was fixed in 10% buffered formalin and processed for histology. Sections of paraffin-embedded tissues were stained with hematoxylin and eosin using standard methods. The first 6 mice in each treatment group were evaluated (total=30 mice). Hepatocyte steatosis (micro- and macro-vesicular fatty change) was mostly limited to zones II/III in control mice; this degree of steatosis was arbitrarily assigned a grade (score) 2. Other samples were graded in a blinded manner (a grade 0 assigned to the lowest degree of steatosis observed). In addition, lipid-laden perisinusoidal cells, presumably stellate (Ito) cells, were observed in mice treated with either PEG-Compound 2 or Compound 170, but not Vehicle in which the Ito cells were obscured by hepatocyte steatosis. The abundance of the Ito cells was evaluated in a blinded manner (without counting) and each sample was arbitrarily graded to provide a semi-quantitative assessment (with a score of 3 indicating the highest abundance).

Both doses of both compounds significantly reduced fed glucose to normoglycemic levels (data not shown), and significantly reduced plasma insulin and HbA1c (data not shown). Significant increases in high molecular weight (HMW) adiponectin vs. vehicle were observed from Day 8 through Day 21, with a trend for dose-dependence, while plasma total adiponectin demonstrated some small, but inconsistent increases vs. vehicle (data not shown). Plasma NEFA and β -OH-butyrate both increased with both compounds (especially at the high dose) vs. vehicle (data not shown), suggesting increased fatty acid oxidation. Significant decreases in both absolute liver weight and liver weight corrected for body weight were observed on Day 21 in all treatment groups (FIGS. 71A and 71B). Specifically, in all four groups treated with FGF-21 variants, absolute liver

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weight was significantly decreased ($p<0.0001$) relative to vehicle control, and the higher dose of PEG-Compound 2 significantly decreased absolute liver weight relative to the lower dose of that compound ($p<0.05$) (FIG. 71A). Additionally, in all four groups treated with FGF-21 variants, the ratio of liver weight to body weight was significantly decreased ($p<0.0001$) relative to vehicle control (FIG. 71B). A dose-dependent reduction in the severity of hepatocyte steatosis was observed in mice treated with either PEG-Compound 2 or Compound 170 compared to vehicle (Table 31). Lipid-laden perisinusoidal cells (presumably Ito or hepatic stellate cells) were observed in sections from PEG-Compound 2 and Compound 170 treated mice (Table 32), but they could not be visualized in sections from Vehicle-treated mice due to interference from hepatocyte steatosis. A dose-dependent reduction in the severity of Ito cell prominence was observed in sections from mice treated with either PEG-Compound 2 or Compound 170.

TABLE 31

Hepatocyte steatosis (Fatty change) Incidence and Histology Scores in ob/ob mice					
	Vehicle	PEG-Compound 2 (8.14 nmol/kg)	Compound 170 (81.45 nmol/kg)	PEG-Compound 2 (81.45 nmol/kg)	Compound 170 (81.45 nmol/kg)
Score	6	6	6	6	6
0	—	—	1	6	6
1	—	6	5	—	—
2	6	—	—	—	—

TABLE 32

Perisinusoidal Lipid-laden Cell Incidence and Histology Scores in ob/ob mice.					
	Vehicle	PEG-Compound 2 (8.14 nmol/kg)	Compound 170 (81.45 nmol/kg)	PEG-Compound 2 (81.45 nmol/kg)	Compound 170 (81.45 nmol/kg)
Score	6	6	6	6	6
0	ND	—	—	1	—
1	ND	—	1	4	1
2	ND	—	—	1	5
3	ND	6	5	—	—

SEQUENCE LISTING

The patent contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US10377806B2>). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed is:

1. A method of treating a disease associated with fibrosis selected from non-alcoholic steatohepatitis (NASH), liver

fibrosis, or cirrhosis comprising administering to a patient in need thereof an effective amount of a modified FGF-21 polypeptide comprising the polypeptide of SEQ ID NO:201,